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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,622	03/16/2004	Chang-Yi Lin	LINC3186 CIP/EM	9676

23364 7590 09/22/2008

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
09/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,622	LIN ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-20 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-20 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The receipt of Information Disclosure Statement dated 03/29/2005 is acknowledged.

Status of claims:

Claims 1-16, 18-20 and 72 are pending in the application.

The rejections that are not reiterated in the current office actions are withdrawn.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 1-15, 18-20 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuno Ichirou JP 64-040418 (Masuno) in view of Willi Paul et al., Porous Hydroxyapatite Nanoparticles for Intestinal Delivery of Insulin, Trends in Biomaterials & Artificial Organs, Volume 14, number 2, 2001 Pages 37-38 (Willi) and in view of Tsuru et al. EP 376331 (Tsuru) and further in view of Sapiezsco et al. US 6383519 (Sapiezsco).

2. Masuno teaches a sustained release material for a drug, obtained by sterilizing a porous substance having biocompatibility, e.g. hydroxycalcium apatite, as an inorganic substance, 2-hydroxyethyl methacrylate or PVA as an organic substance or chitin, chitosan or collagen as a natural high polymer, dipping the sterilized porous substance in a solution of the drug dispersed in a solvent, decompressing the porous substance to remove air in pores of the porous substance, permeating the drug into all the pores and adsorbing the drug on the surface thereof. The above-mentioned sustained release material is embedded in a body to directly contact affected parts of the vicinity thereof and impart the drug effects of sustained release to affected parts (abstract).

Masuno's abstract does not include the size and surface area of the pores.

Willi teaches the encapsulation of insulin, hyaluronic acid and sodium alginate in porous hydroxyapatite wherein the pore size is less than 10 micron.

It would have been obvious to a person having ordinary skill in the art to follow the pore size disclosed by Willi since the reference has the same endeavor.

Neither of the references teaches the Ca/P ratio and the surface area of the pores.

Tsuru teaches drug delivery granules comprising porous granules of a calcium phosphate compound having a ratio of Ca to P of 1.3 to 1.8 (examples disclose a ratio of 1.67, and 1.5), a porosity of 0.1 to 70%, a specific surface area of 0.1 to 50 m^2/g and a pore size of 1nm to 10 microns (abstract, page 3, lines 31-40 for preferable ratios and surface areas, and see also examples). The polymer comprised can be gelatin, carboxymethylchitin, glycol chitin and the like (page 4, lines 45+). The invention includes different types of the drugs such as carcinostatics, antibiotics and the like (page 4, lines 56+).

It would have been obvious to a person having ordinary skill in the art to use surface area and Ca/P ratio disclosed by Tsuru because both disclosures discuss the same field of art and Tsuru teaches that the drug delivery granules of the invention has a controllable and good prolonged effect of the drug release (abstract).

Regarding the amount of polymer and/or the amount of drug loaded, since Masuno teaches that the apatite should be decompressed to remove the air from the pores, consequently, the amount of entrapped material in the pores can be controlled through this decompression and the amount of drug loading should be within the capabilities of a person of ordinary skill in the art.

None of the references teaches the use of further biocompatible polymer.

Sapiezsco teaches methods for the preparation of porous inorganic shaped bodies especially calcium phospliate-containing shaped bodies. The solution is absorbed into a porous

sacrificial substrate such as a cellulose sponge. The shaped bodies include Hydroxyapatite and are used as drug delivery vehicle. The reference teaches that the structure comprises bioabsorbable polymer or film-forming agent such as polyglycolic acid (PGA), poly-L-Lactic acid (PL-LA) (see col.24, lines 31+). The reference also discloses that the pores may be partially or completely filled a medicament such as growth hormone, antibiotic, cell signaling material, or the like (col. 12, lines 45-49).

it would have been obvious to one of ordinary skill in the art at the time the invention was made to add one of the bioabsorbable polymer or film-forming agent such as polyglycolic acid (PGA), poly-L-Lactic acid (PL-LA) because Sapiezsco discloses that these polymers renders the structure mass is strong, carveable, and somewhat compressible (col. 24, lines 41-42).

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masuno Ichirou JP 64-040418 (Masuno) in view of Willi Paul et al., Porous Hydroxyapatite Nanoparticles for Intestinal Delivery of Insulin, Trends in Biomaterials & Artificial Organs, Volume 14, number 2, 2001 Pages 37-38 (Willi), Tsuru et al. EP 376331 (Tsuru).and further in view of Troczynski US 6730324 (Troczynski).

Masuno, Willi, and Tsuru have been discussed above.

None of the references disclosed the drugs recited in claim 16.

Troczynski teaches novel room-temperature process for obtaining calcium phosphate, in particular hydroxyapatite, coatings and microspheres that encapsulate drugs (abstract). Among the drugs used in the invention anti-inflammatory agents which is a generic disclosure of aspirin and ibuprofen (see example 4).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate anti-inflammatory drugs in hydroxyapatite structure because Troczynski

teaches that these drugs have an advantage that if anti-inflammatory agents were incorporated into the implant devices to avoid acute or severe inflammatory response (example 4).

Regarding new claim 72, the size of the grain overlaps with Willi and the other limitations of pore size, surface area, and the Ca/P ration overlaps with Tsuru. The polymers recited in the claims are known biocompatible polymers that are well known in the art; note that Sapiezsco discloses polyvinyl alcohol which is imbibed in the porous apatite. Thus, the whole invention is prima facie obvious to a person having ordinary skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the sustained release porous Hydroxyapatite material to deliver a drug of Masuno and apply the pore size, the surface area of the pores and the Ca/P ratio of Tsuru because Tsuru's invention is the same field and has the same aim. It would have been also obvious to one of ordinary skill in the art to include polyglycolic acid (PGA), poly-L-Lactic acid (PL-LA) because Sapiezsco discloses that these polymers renders the structure mass is strong, carveable, and somewhat compressible. The skilled artisan would include anti-inflammatory drugs in the invention to avoid acute or severe inflammatory response to the apatite structure. The expected result would be a stable pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains.

Response to Arguments

1. Applicant's arguments filed 4/28/2008 have been fully considered but they are not persuasive. Applicant argues that:

- The "porous granules of a calcium phosphate compound" in Tsuru, for example, the porous hydroxyapatite granules used in Examples 1-4, 6-7 and "porous tricalcium phosphate (TCP)" in Example 5 of D1, is not the "porous apatite grains" recited in claim 1 of the present application, because the former is a porous calcium phosphate compound prepared by firing at

a temperature of 200-1400°C, preferably 500-1300°C, and more preferably 700-1200°C with a forming agent or a particulate substance capable of being dissipated upon heating (page 3, lines 14-30); and the latter is prepared by incubation of wetted granules of a slurry containing particles of a calcium source and particles of a phosphate source (please see claims 21 or 48 of the present application).

To respond: Applicant is arguing that the method of preparing the instant composition should differentiate it over the prior art. It is noted that claims 21 or 48 to which applicant refers are cancelled claims. Further, regardless of the method the granules disclosed by Tsuru are having a slow release drug delivery comprising porous granules of calcium phosphate. In addition, in the current office action Tsuru is relied upon fro teaching the Ca/P ratio and the surface area of the pores.

- The polymer used by Tsuru as disclosed in page 4, lines 45+, is for lowering the specific gravity of the calcium phosphate granules, which is done by coating the polymer on the calcium phosphate granules after the calcium phosphate granules being formed. On the contrary, the biocompatible polymer is located among the porous apatite grains to bind them into a microspherical composite in the subject invention. This microspherical composite structure is prepared by special processes as recited in claims 40 and 66 of the present application.

To respond: Tsuru teaches the same polymers such as chitins and gelatin. It is clear that same compounds have same properties. Even if Tsuru uses the polymer for another reason, the polymer would still accrue its properties in all compositions.

- The major difference between Tsuru and the newly amended claim 1 of the present application is the former discloses a porous calcium phosphate compound bulk and disintegrate the bulk into porous granules which can be further coated with a polymer, and the latter

discloses a microspherical composite composed of porous apatite grains bounded by a polymer in the a microspherical composite and among the porous apatite grains.

To respond: in view of withdrawing the rejection under 35 USC §102, the arguments is rendered moot.

- Masuno is not close to the subject invention, because it discloses a porous substance of hydroxycalcium apatite or a natural high polymer. As recited in claim 2 of Masuno the porous substance of hydroxycalcium apatite is a calcined hydroxycalcium apatite, and this is not close to the porous apatite grains of the subject invention as explained in above 1).

To respond: instant claim 1 recites generic porous apatite grains. Masuno teaches porous hydroxycalcium apatite (see abstract). Thus Masuno's apatite is encompassed by the apatite of instant claims.

- Willi Paul et al prepare hydroxyapatite nanoparticles by firing CHA (chitosan-HA) particles at 800°C for one hour to remove chitosan. (Please see page 2, lines 18-29, "Materials & Methods"). That means the hydroxyapatite nanoparticles disclosed by Willi Paul et al are not porous apatite grains as recited in the newly amended claim 1 as explained in above 1). Moreover, these are not obvious to one of ordinary skill in the art to which the invention pertains.

To respond: Willi Paul teaches the encapsulation of insulin, and hyaluronic acid in porous hydroxyapatite wherein the pore size is less than 10 micron. Thus Willi Paul teaches the same apatite grains and the same polymer recited in claim 8. The method of preparing the instant claims and the difference between prior art methods would not be of weight since determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by- process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process (See MPEP 2113).

- Sapiezsco is not close to the subject invention because it discloses a porous scaffold structure, which is not the porous apatite grains of the subject invention. This porous scaffold structure in Sapiezsco may be imbibed with biosasorbable polymer or film-forming agent such as PGA, PL_PA (see col. 24, lines 31+), which is not a microspherical composite composed of porous apatite grains bounded by a polymer in the microspherical composite and among the porous apatite grains.

To respond: Sapiezsco teaches that the the shaped bodies produced may be comminuted to yield highly useful and unique powder materials finding wide utility. Such powders are very small. Thus, this invention provides highly uniform inorganic materials in powder form having particle sizes, measured by light scattering techniques such that the number mean size is between about 0.1 and 5.0 .mu.m. Particle sizes between about 0.5 and 2.0 .mu.m may also be attained (col. 14, lines 3+). Note also that Sapiezsco teaches that the composition prepared is porous (see abstract). Thus, the reference teaches porous apatite particles.

- The rejection of claim 16 under 35 USC 103(a) as being unpatentable over Masuno Ichirou in view of Willi Paul et al., Tsuru et al., and further in view of Troczynski has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the above comments.

To respond: Applicant does not argue Troczynski to explain why the rejection is traversed.

Conclusion

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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